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The Medical Research Council chronic dyspnea score predicts the survival of patients with idiopathic pulmonary fibrosis

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Summary
Background: The Medical Research Council (MRC) chronic dyspnea scale (6-point) is used in different clinical conditions to grade breathlessness on daily activities. We have previously shown that in patients with histologically documented usual interstitial pneumonia/idiopathic pulmonary fibrosis (UIP/IPF), the MRC dyspnea scale is useful in estimating disease severity. The aim of this study was to further investigate the usefulness of the MRC scale in IPF as a marker of survival.
Methods: The records of 25 patients with histologically documented UIP/IPF were retrospectively reviewed. Clinical parameters, pulmonary function tests, and arterial blood gases at the time of diagnosis, as well as survival time were retrieved and recorded for each patient. The impact of the different variables determined at diagnosis on survival was examined using the Kaplan–Meier and uni- and multi-variate Cox-regression analyses.
Results: Among the baseline clinical and physiologic parameters determined at the time of IPF diagnosis, the MRC score, the Tiffeneau index, and the total lung capacity were the only significant and independent predictors of survival. In specific, a high MRC score, a high Tiffeneau index, and a low total lung capacity at presentation were associated with shorter survival.

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Conclusion: In accordance with the previous work, our results indicate that the Tiffeneau index and total lung capacity (TLC) are the important determinants of survival in patients with IPF. In addition, we show that the simple MRC chronic dyspnea score estimated at the time of diagnosis is equally predictive of survival and may aid clinicians in assessing the prognosis of new cases of IPF.

Introduction

In idiopathic pulmonary fibrosis (IPF), a combination of inflammatory and fibrotic lung parenchymal damage leads to the defects in lung mechanics and gas exchange which manifest clinically with progressive exertional dyspnea, the most prominent and disabling symptom in these patients.[1–4] Since IPF carries a poor prognosis, early prediction of survival is of considerable value for clinicians. Recent studies have shown that among the noninvasive variables used to estimate disease severity, the total lung capacity (TLC) and forced vital capacity (FVC) are independent predictors of IPF outcome.[5–7] However, additional simple clinical tools to estimate prognosis are useful, as not all patients with IPF are fit to execute lung function testing maneuvers.

The Medical Research Council (MRC) chronic dyspnea scale is commonly used to grade breathlessness in patients suffering from various clinical conditions.[8–13] We have previously shown that, in patients with IPF, the MRC score is helpful in estimating disease severity, since the score correlated with both physiologic and radiologic indices of disease severity and extent.[12]

The aim of this study was to examine whether clinical and physiologic parameters recorded during the diagnosis of IPF, including the MRC chronic dyspnea score, can serve as surrogate predictors of survival. We hypothesized that, in addition to the lung function tests, the MRC index would be tightly linked to survival.

Patients and methods

Subjects

This study was approved by the Institutional Ethics Committee of ''Attikon'' University Hospital, National and Kapodistrian University of Athens, Greece. Written informed consent was obtained from each patient. We retrospectively reviewed the records of 25 consecutive patients with IPF, who were recruited from the respiratory outpatient clinic between the years 2004 and 2007. Some of these patients have been included in a previous study of our group.[12] All patients had IPF based on ATS/ERS diagnostic criteria and lung biopsies obtained by video-assisted thoracoscopic surgery, which showed usual interstitial pneumonia (UIP).[4] Secondary causes of lung fibrosis were excluded: none of the patients had a history of environmental or occupational exposure, drug toxicity or connective tissue disease, as documented by history, clinical and immunological tests. Upon establishment of the diagnosis, all patients received initially oral methylprednisolone (0.3 mg/kg/d with subsequent taper) and azathioprine (3 mg/kg/d) for at least 3 months.[4] One patient was treated with oral colchicine (0.6 mg/d) in addition to immunosuppressants.

Dyspnea

Dyspnea was assessed at presentation by the treating physicians (EDM, ZD, SAP) using the self-administered 6-point MRC chronic dyspnea questionnaire consisting of the following questions about perceived breathlessness: 0, no dyspnea; 1, slight dyspnea (shortness of breath when hurrying on the level or walking up a slight hill); 2, moderate dyspnea (walks slower than people of the same age on the level because of breathlessness); 3, moderately severe dyspnea (stops because of breathlessness when walking at own pace on the level); 4, severe dyspnea (stops for breath after walking about 100 yards or after a few minutes on the level); 5, very severe dyspnea (too breathless to leave the house or breathless when dressing or undressing).[8]

Pulmonary function tests

Lung function tests were done during the diagnostic approach and included forced expiratory volume during the 1 s of expiration (FEV_1), forced vital capacity (FVC), FEV_1/FVC (Tiffeneau) index, TLC, and single-breath carbon monoxide diffusing capacity (DLCO). TLC was measured by the helium dilution method with a Master Screen apparatus (Erich Jaeger GmbH, Wuerzburg, Germany) and DLCO by the single breathholding helium dilution method.[14,15] Measurements were expressed as percent of predicted normal values.[14,15] The arterial partial pressure for oxygen (PaO_2) and carbon dioxide ($PaCO_2$) were also measured at rest in all patients.

Survival

At the time of data acquisition for this study, 12/25 patients had succumbed to IPF. All deaths were directly attributable to the disease, a fact verified by death certificates. The 13/22 patients still alive during reporting of this work were censored for survival analysis.

Statistics

Normally and not normally distributed data are presented as mean $\pm$ SEM or median (interquartile range), respectively. Survival is given as median or mean (95% confidence interval); mean was used when median survival could not be calculated (e.g. when more than half of the observations were censored). *n* indicates the number of observations.

Table 1 Data acquired during the study.

No.	Age (yr)	Sex	Smoking (pck-yr)	Symptoms (mos)	MRC	Survival (mos)	FEV_1 (% predicted)	FVC (% predicted)	FEV_1/FVC (% predicted)	TLC (% predicted)	DL (% predicted)	PaO_2 (mmHg)	$PaCO_2$ (mmHg)
1	60	1	0	60	3	16*	75	64	92	50	22	70	35
2	70	1	20	12	1	78*	97	80	93	62	54	78	45
3	70	1	0	14	2	59*	61	60	78	52	52	62	35
4	56	1	45	60	2	80	63	56	89	52	48	71	37
5	55	0	0	10	1	97	97	94	87	74	80	80	37
6	49	0	0	18	2	52*	97	87	90	68	32	77	30
7	43	0	60	20	2	69	77	77	84	74	38	76	31
8	67	0	0	9	1	90	90	90	81	68	56	88	38
9	64	0	0	6	1	68	89	87	87	70	55	84	37
10	69	1	60	4	1	68	94	85	84	69	74	74	39
11	63	0	0	12	4	6*	77	67	94	51	35	73	30
12	64	1	40	60	3	8*	70	55	100	46	43	72	39
13	62	0	0	30	2	9*	87	75	95	55	50	75	38
14	41	1	2	30	2	85*	92	84	91	74	70	87	42
15	71	0	0	21	2	100	78	85	75	96	54	75	38
16	80	1	15	12	1	33*	92	77	88	61	61	89	43
17	60	1	10	6	3	70	70	56	98	90	63	72	38
18	70	1	15	24	3	76	61	68	79	52	51	66	40
19	73	1	50	18	4	54*	57	64	89	49	31	72	38
20	64	1	0	12	2	37*	83	69	94	53	46	69	39
21	73	0	0	6	1	50	76	65	97	51	21	78	41
22	60	0	0	20	5	7*	69	56	100	87	78	49	28
23	67	0	0	8	2	53	78	75	91	67	45	70	39
24	80	0	0	12	3	3	84	81	93	65	36	77	43
25	68	0	0	15	3	46	86	78	92	67	24	57	42

MRC, Medical Research Council dyspnea score; FEV_1, forced expiratory volume during the 1 s of expiration; FVC, forced vital capacity; TLC, total lung capacity; DL, single-breath carbon monoxide diffusing capacity; PaO_2, arterial partial oxygen pressure; $PaCO_2$, arterial partial carbon dioxide pressure.

*Patients that succumbed to IPF; the rest of survival data represent censored observations.

Survival analysis was done in two ways: (i) Kaplan–Meier analysis with log-rank tests for comparisons between groups was performed after splitting the study cohort into groups according to the variable under examination for impact on survival. When the variable was not categorical (such as e.g. sex or MRC), arbitrary cut-off points were used. In the case of lung function tests, the limits of normal were used as cut-off points. In all other cases, median values were used to divide the study cohort in two groups. (ii) Simple (univariate) and multiple (multivariate) Cox regression (risk ratio) analyses were employed. Probability values less than 0.05 were considered statistically significant. All analyses were done using the Statistical Package for the Social Sciences Software Version 11.0 (SPSS, Chicago, IL).

Results

The demographic, clinical, and functional characteristics of the study population at the time of IPF diagnosis are given in Tables 1 (raw data) and 2 (summarized data).

At the time of reporting of this study, 12 patients had succumbed to IPF while 13 patients were still alive (Table 1 and Figure 1). Initially, we examined whether any of the parameters determined at diagnosis were linked to survival using Kaplan–Meier analysis. In this regard, age, sex, smoking status and exposure, symptom duration before diagnosis, and arterial blood partial gas tensions were not associated with survival (Table 2). On the contrary, patients with higher MRC scores at diagnosis exhibited significantly shorter survival (Figure 2A). In addition, patients with low FVC (<80% predicted), high FEV_1/FVC ratio (⩾90% predicted), and low TLC (<65% predicted) at presentation, experienced shorter survival (Figure 2B–D). There was no apparent link between FEV_1 and DLCO at presentation and survival.

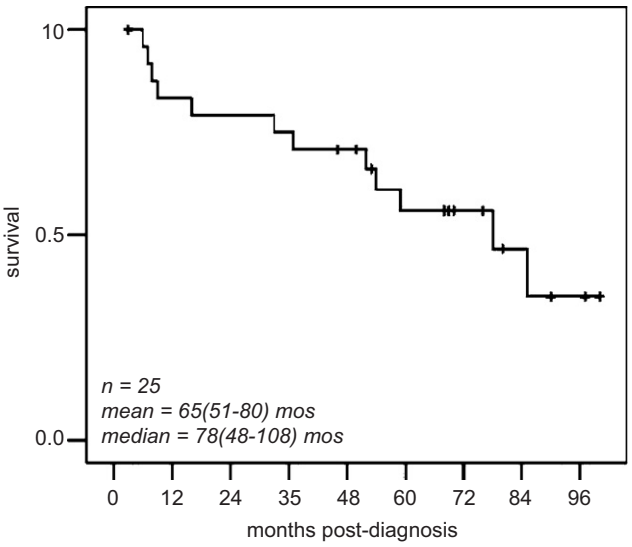

Figure 1 Survival of 25 patients with histologically documented UIP/IPF. Twenty-five patients with histologically documented UIP/IPF were followed till death (uncensored: $n = 12$) or reporting of the study (censored: $n = 13$). Shown are cumulative Kaplan–Meier survival plot, sample size (n), and survival [mean and median (95% confidence interval)].

Table 2 Summary of baseline characteristics of 25 patients with histologically documented IPF and their impact on survival using univariate Cox-regression analysis.

	Trend	*P*	RR (95% CI)
Age (years)†	64±2	0.800	1.008 (0.951–1.068)
Sex (male/female)	12/13	0.278#	
Smoking (never/ex-/current)	15/5/5	0.927#	
(pack-years)†	13±4	0.597	0.992 (0.961–1.023)
Symptom duration (months)††	14 (10–21)	0.167	1.022 (.991–1.053)
MRC dyspnea score††	2 (1–3)	0.007*	2.290 (1.257–4.170)
Lung function tests (% predicted)†			
FEV_1	80±2	0.628	0.989 (0.947–1.034)
FVC	73±2	0.046*	0.950 (0.904–0.999)
FEV_1/FVC	90±1	0.011*	1.162 (1.035–1.304)
TLC	64±3	0.032*	0.935 (0.879–0.994)
DLCO	49±3	0.209	0.975 (0.936–1.015)
Arterial blood gases (mmHg)†			
PaO_2	74±2	0.167	0.951 (0.886–1.021)
$PaCO_2$	38±1	0.170	0.898 (0.770–1.047)

†Data presented as mean±standard error of mean.
††Data presented as median (interquartile range).
*Significant predictors of survival among baseline features of study cohort.
#Log-rank test for comparison of survival between male and female patients or never/former/current smokers using Kaplan–Meier analysis.
MRC, Medical Research Council; FEV_1, forced expiratory volume during the 1 s of expiration; FVC, forced vital capacity; TLC, total lung capacity; DLCO, single-breath carbon monoxide diffusing capacity; PaO_2, arterial partial oxygen pressure; $PaCO_2$, arterial partial carbon dioxide pressure; RR, risk ratio; CI, confidence interval.

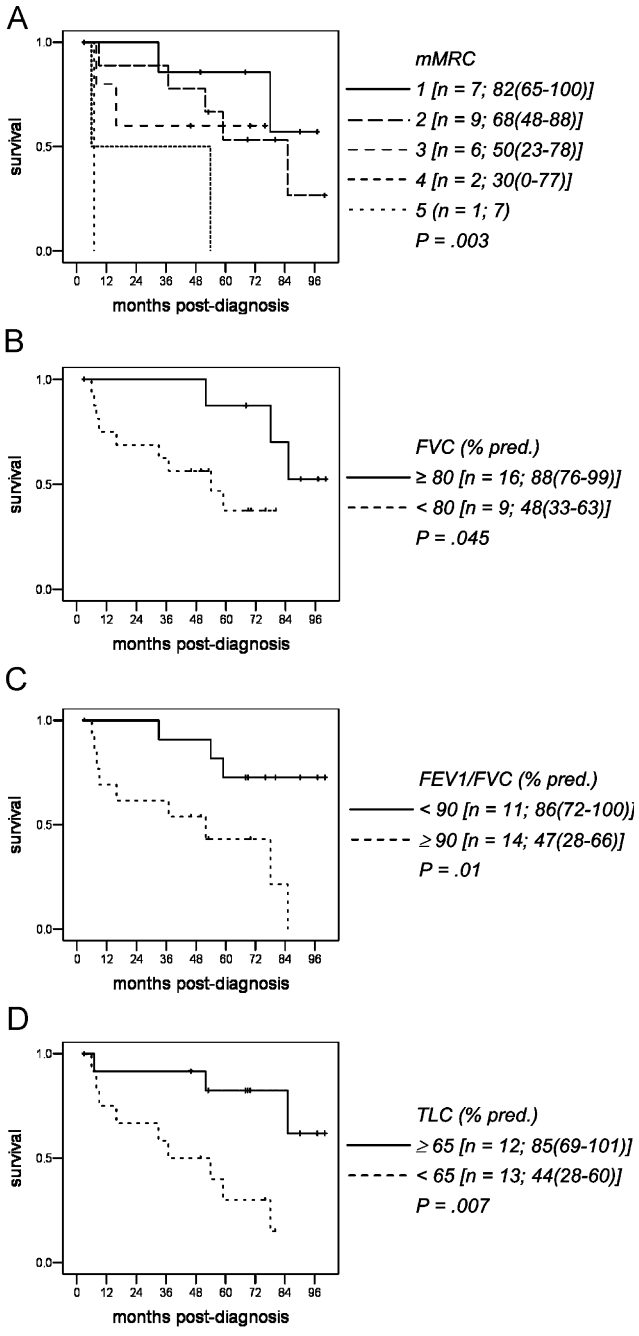

Figure 2 Baseline parameters at IPF diagnosis that are linked to survival using Kaplan–Meier analysis. Twenty-five patients with histologically documented UIP/IPF were clinically and functionally assessed during diagnosis and were followed till death (uncensored: $n = 12$) or reporting of the study (censored: $n = 13$). (A) Patients with higher initial MRC scores experienced shorter survival. (B) Patients with FVC $<$ 80% (C), FEV_1/FVC $\geqslant$ 90% (D), and TLC $<$ 65% of predicted values exhibited significantly shorter survival. Shown are cumulative Kaplan–Meier survival plots, sample sizes (n), mean (95% confidence interval) survival times, and log-rank test probability values (P) for comparison between groups. IPF, idiopathic pulmonary fibrosis; MRC, Medical Research Council. FEV_1, forced exhaled volume in the first second of exhalation; FVC, forced vital capacity; TLC, total lung capacity.

Table 3 Impact of MRC, FVC, FEV_1/FVC, and TLC on survival using multivariate Cox regression analysis.

	P	RR (95% CI)
MRC dyspnea score	0.022*	2.394 (1.133–5.058)
Lung function tests (% predicted)		
FVC	0.033	1.045 (0.956–1.142)
FEV_1/FVC	0.017*	1.246 (1.039–1.494)
TLC	0.024*	0.929 (0.871–0.990)

*Significant predictors of survival among baseline features of study cohort.
MRC, Medical Research Council; FEV_1, forced expiratory volume during the first second of expiration; FVC, forced vital capacity; TLC, total lung capacity; RR, risk ratio; CI, confidence interval.

On univariate Cox-regression analysis (Table 2), low initial FVC and TLC, and high initial FEV_1/FVC ratio significantly and negatively impacted survival, in accord with the Kaplan–Meier analyses detailed above. Importantly, the MRC score was the only purely clinical-derived indicator independently predicting survival. We then entered these variables (FVC, FEV_1/FVC index, TLC, and MRC score) in multiple Cox regression analyses to generate a linear model. FVC did not emerge as an independent prognosticator of outcome in IPF. However, along with the FEV_1/FVC index and TLC, the MRC score proved to be an independent predictor of survival (Table 3). Collectively these results indicate that the MRC score recorded at diagnosis of IPF may serve as an independent predictor of survival, along with functional variables, such as the FEV_1/FVC index and TLC.

Discussion

In this study we assessed dyspnea at diagnosis in 25 patients with histology-proven UIP/IPF, using a simple self-reported questionnaire, the MRC chronic dyspnea score.[8] We also measured the physiologic parameters commonly used to assess disease severity, including the lung function tests and arterial blood gases. In our patients with IPF, the FEV_1/FVC index and TLC could independently predict survival. In addition, the MRC score was the only pure clinical parameter that could serve as an independent predictor of survival. We have previously shown that in patients with IPF, the MRC score determined at presentation is a marker of disease severity.[12] The present study suggests that this simple clinical measurement can also be used as a marker of survival in IPF patients.

We have previously shown that in patients with IPF, the MRC index determined at diagnosis is intimately associated with the degree of disease severity, independently so with the FEV_1/FVC index and TLC.[12] In the present study we have found that these indices of disease severity that are independently linked to the MRC score were also predictive of survival. Hence, not only the MRC score can predict survival in patients suffering from IPF, but so can the baseline parameters intimately associated with this index.

IPF is a chronic and progressive interstitial lung disease that uniformly results in severe disability and death.[1–3] Virtually every affected person will develop breathlessness at rest or with minimal exertion as the disease advances.[13,16,17] Previous studies that attempted to predict prognosis in IPF and other fibrogenic interstitial pneumonias have focused on baseline physiologic, radiographic, and clinical parameters and have yielded inconsistent or contradictory results.[18–23] Other more elaborate scores identified the histopathologic pattern as an important baseline predictor of survival.[24–27] However, the risks of biopsy are not negligible, and nowadays there is a tendency to rely more on a constellation of clinical and imaging findings indicative of UIP/IPF, obviating biopsy.[28,29] In addition, clinicians facing patients with UIP/IPF are in need of simpler and safer approaches to predict survival. Herein we show that the MRC index can be used for this purpose.

As far as the population of our study is concerned, all of our patients had histologically based diagnoses of UIP/IPF, meaning that heterogeneity of pathological types of interstitial lung disease could not have influenced our findings. Our patients presented with age, gender, pulmonary function, and DLCO similar to study cohorts reported by others.[6,7] Differences were seen in smoking habits, FEV_1/FVC, and treatment. Most of our patients were never- or ex- smokers, presented with a more restrictive pattern of disease, and had mostly been treated with azathioprine plus prednisone. Most importantly however, their mean age (64 ± 2years) was not outside the transplant age-line.[30]

In our IPF patients, the MRC score assessed at diagnosis of IPF was the only purely clinical predictor of survival. Compared to previously reported scores for IPF progression, such as the clinical, radiographic and physiologic (CRP) score, the MRC score is by far the simplest.[31–33] Previous early studies provided short-term validation for CRP, but longitudinal studies suggested significant variability.[31,34] This suggests the need to extend the use of the MRC score in larger prospective trials in IPF patients. Although our results are based on a retrospective analysis of a relatively small number of patients, the present study was done on a solid group of biopsy proven UIP/IPF patients and all deaths were IPF-related.

It is a common belief that the predictive value of easily measured, safely performed and reliable clinical and physiologic parameters could improve the care of patients with IPF in several ways. It could allow clinicians to make a accurate prognosis and facilitate a timely referral of patients with limited prognosis for lung transplantation.[7,34] In this regard, it was recently shown that lung transplantation is the only therapy to prolong survival in advanced IPF. However, a major factor leading to increased death rates among this patient group on the transplant waiting list is referral delay due to a lack of validated prognostic measures.[35,36] In this study we show the usefulness of the MRC chronic dyspnea scale in predicting the survival of patients suffering from IPF relatively at the early course of the disease. Hence the MRC index may be useful in patient selection for timely referral for transplantation.

In conclusion, our data indicate that the MRC index is not only a good indicator of disease severity, but also of survival in IPF. A larger prospective study is still needed to better elucidate the relationship between physiological changes, survival, and the MRC score in UIP/IPF patients.

Competing interest statement

All authors declare that no financial or other potential competing interests exist with the study matter.

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References

1. Katzenstein AL, Zisman AD, Litzky AL, Nguyen BT, Kotloff RM. Usual interstitial pneumonia. Histologic study of biopsy and explant specimens. *Am J Surg Pathol* 2002;**26**:1567–77.
2. Flaherty KR, Travis WD, Colby TV, et al. Histopathologic variability in usual and nonspecific interstitial pneumonias. *Am J Respir Crit Care Med* 2001;**164**:1722–7.
3. Selman M, King Jr TE, Pardo A. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications therapy. *Ann Intern Med* 2001;**134**:136–51.
4. American Thoracic Society. European Respiratory Society, American College of Chest Physicians. Idiopathic pulmonary fibrosis, diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med* 2000;**161**:646–64.
5. Latsi P, Du Bois R, Nicholson A, et al. Fibrotic idiopathic interstitial pneumonia. The prognostic value of longitudinal trends. *Am J Respir Crit Care Med* 2003;**168**:531–7.
6. Flaherty KR, Mumford JA, Murray S, et al. Prognostic implications of physiologic and radiographic changes in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;**168**:543–8.
7. Collard HR, King Jr T, Bartelson BB, Vourlekis JS, Schwartz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;**168**:538–42.
8. Eltayara L, Becklake MR, Volta CA, Milic-Emili J. Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;**154**:1726–34.
9. Bestall JC, Paoul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;**54**:581–6.
10. Koulouris NG, Retsou S, Kosmas E, et al. Tidal expiratory flow limitation, dyspnoea and exercise capacity in patients with bilateral bronchiectasis. *Eur Respir J* 2003;**21**:743–8.
11. Delclaux C, Zerah-Lancner F, Bachir D, et al. Factors associated with dyspnea in adult patients with sickle cell disease. *Chest* 2005;**128**:3336–44.
12. Papiris SA, Daniil Z, Malagari K, et al. The Medical Research Council dyspnea scale in the estimation of disease severity in idiopathic pulmonary fibrosis. *Respir Med* 2005;**99**:755–61.
13. Tzanakis N, Samiou M, Lambiri I, Antoniou K, Siafakas N, Bouros D. Evaluation of health-related quality-of-life and dyspnea scales in patients with idiopathic pulmonary fibrosis. Correlation with pulmonary function tests. *Eur J Intern Med* 2005;**16**:105–12.
14. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report working party, standardization of lung function tests, European Community for Steel and Coal. Official statement of the

European Respiratory Society. *Eur Respir J* 1993;**6**(Suppl. 16): S5–S40.
15. Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC. Standardization of the measurement of transfer factor (Diffusing Capacity). Report working party, standardization of lung function tests, European Community for Steel and Coal. Official statement of the European Respiratory Society. *Eur Respir J* 1993;**6**(Suppl. 16):S41–52.
16. Martinez TY, Pereira CA, dos Santos M, Ciconelli RM, Guimaraes SM, Martinez JA. Evaluation of the short form 36-item questionnaire to measure health-related quality of life in patients with idiopathic pulmonary fibrosis. *Chest* 2000; **117**:1627–32.
17. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest* 1988;**93**:580–6.
18. Gay SE, Kazerooni EA, Toews GB, et al. Idiopathic pulmonary fibrosis: predicting response to therapy and survival. *Am J Respir Crit Care Med* 1998;**157**:1063–72.
19. Erbes R, Schaberg T, Loddenkemper R. Lung function tests in patients with idiopathic pulmonary fibrosis. Are they helpful for predicting outcome? *Chest* 1997;**111**:51–7.
20. Schwartz DA, Scott van Fossen D, Davis CS, et al. Determinants of progression in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1994;**149**:444–9.
21. Hubbard R, Johnston I, Britton J. Survival in patients with cryptogenic fibrosing alveolitis. A population-based cohort study. *Chest* 1998;**113**:396–400.
22. Mogulcoc N, Brutsche MH, Bishop PW, Greaves M, Horrocks AW, Egan JJ. On behalf of the greater manchester pulmonary fibrosis consortium. Pulmonary function in idiopathic pulmonary fibrosis and referral for lung transplantation. *Am J Respir Crit Care Med* 2001;**164**:103–8.
23. King Jr TE, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med* 2001; **164**:1171–81.
24. King TE, Schwarz MI, Brown K, et al. Idiopathic pulmonary fibrosis: relationship between histopathologic features and mortality. *Am J Respir Crit Care Med* 2001;**164**:1025–32.
25. Nicholson AG, Colby TV, du Bois RM, Hansell DM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med* 2000;**162**:2213–7.
26. Daniil ZD, Gilchrist FC, Nicholson AG, et al. A histologic pattern of nonspecific interstitial pneumonia is associated with a better prognosis than usual interstitial pneumonia in patients with cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med* 1999;**160**:899–905.
27. Nicholson A, Fulford L, Colby T, du Bois RM, Hansell DM, Wells AU. The relationship between individual histologic features and disease progression in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2002;**166**:173–7.
28. Utz J, Ryu J, Douglas W, et al. High short term mortality following lung biopsy for usual interstitial pneumonia. *Eur Respir J* 2001;**17**:175–9.
29. Hunninghake G, Zimmerman M, Schwartz D, et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2001;**164**:193–6.
30. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update; a consensus report from the pulmonary scientific council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2006;**25**:745–55.
31. Martinez FJ, Flaherty K. Pulmonary function testing in idiopathic interstitial pneumonias. *Proc Am Thorac Soc* 2006;**3**: 315–21.
32. Tzanakis N, Samiou M, Lambiri I, Antoniou K, Siafakas N, Bouros D. Evaluation of health-related quality of life and dyspnea scales in patients with idiopathic pulmonary fibrosis. Correlation with pulmonary function tests. *EJIM* 2005;**16**:105–12.
33. Gay S, Kazerooni EA, Toews GB, et al. Idiopathic pulmonary fibrosis. Predicting response to therapy and survival. *Am J Respir Crit Care Med* 1998;**157**:1063–72.
34. King Jr T, Tooze JA, Schwarz MI, Brown K, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis. Scoring system and survival model. *Am J Respir Crit Care Med* 2001; **164**:1171–81.
35. Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med* 2005;**142**:963–7.
36. Walter N, Collard HR, King Jr TE. Current perspectives on the treatment of idiopathic pulmonary fibrosis. *Proc Am Thorac Soc* 2006;**3**:330–8.